SWACSM Abstract

Mitochondrial Integrity Distinguishes Exercise-induced vs. Pathogenic Cardiac Hypertrophy

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ABSTRACT

Cardiac hypertrophy is a consequence of exercise training, as well as certain cardiomyopathies. However, the key genetic drivers of cardiomyocellular remodeling in a healthy vs diseased heart are inadequately understood. **PURPOSE**: Determine the genetic architecture of exercise training-induced cardiomyocellular remodeling and hypertrophy. **METHODS:** The exercise hybrid mouse diversity panel (ExcHMDP) is comprised of 100 strains of Exc trained (TRN) and sedentary (SED) animals (n=4-8/strain per group). After 30d of exercise, running wheels were locked, and 24-hours post-exercise, 6h-fasted animals were euthanized and tissues harvested (~20 tissues/mouse). To interrogate pathogenic cardiac hypertrophy, isoproterenol (ISO, 30mg/kg/day for 21d) was administered to a second HMDP cohort, and similar to TRN hearts, RNAseq analyses were performed. **RESULTS:** TRN increased heart weight in 85% of 100 mouse strains vs. sedentary (SED). Of the nearly thirty heart phenotypes assessed, none correlated significantly with running distance. Interestingly, the heart showed relatively few differentially expressed genes when compared to other tissues (e.g. skeletal muscle and white adipose). Enrichment analysis of differential gene expression revealed mitochondrial function, inflammatory and immune processes, calcium signaling, muscle growth and development, and angiogenesis (FDR<0.05) as top pathways impacted by TRN. Candidate gene identification analysis of TRN-induced cardiac hypertrophy revealed five putative regulatory genes associated with healthy cardiac remodeling: *IL31ra*, *Fam167b*, *Tafa5*, *Crip3*, and *Nanos1* (P<0.01). Biological processes divergent between the Exc and ISO-HMDPs included oxidative phosphorylation, electron transport chain, and mitochondrial respiratory chain complex assembly (FDR<1.1E-07). Electron microscopy analyses of TRN vs. ISO hearts showed differential remodeling of mitochondrial cristae involved in oxidative metabolism. **CONCLUSION**: Our studies provide important insight into the genetic architecture of cardiac remodeling associated with healthy vs. pathogenic hypertrophy. A primary goal is that our transcriptomics analyses are leveraged to advance therapeutics to combat hypertrophic cardiac myopathy-associated heart failure.